Venous Thromboembolic Disease
Long Term Management

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GENERAL HEMATOLOGY
OHSU

DISCLOSURE

Relevant Financial Relationship(s)

Speaker Bureau - None

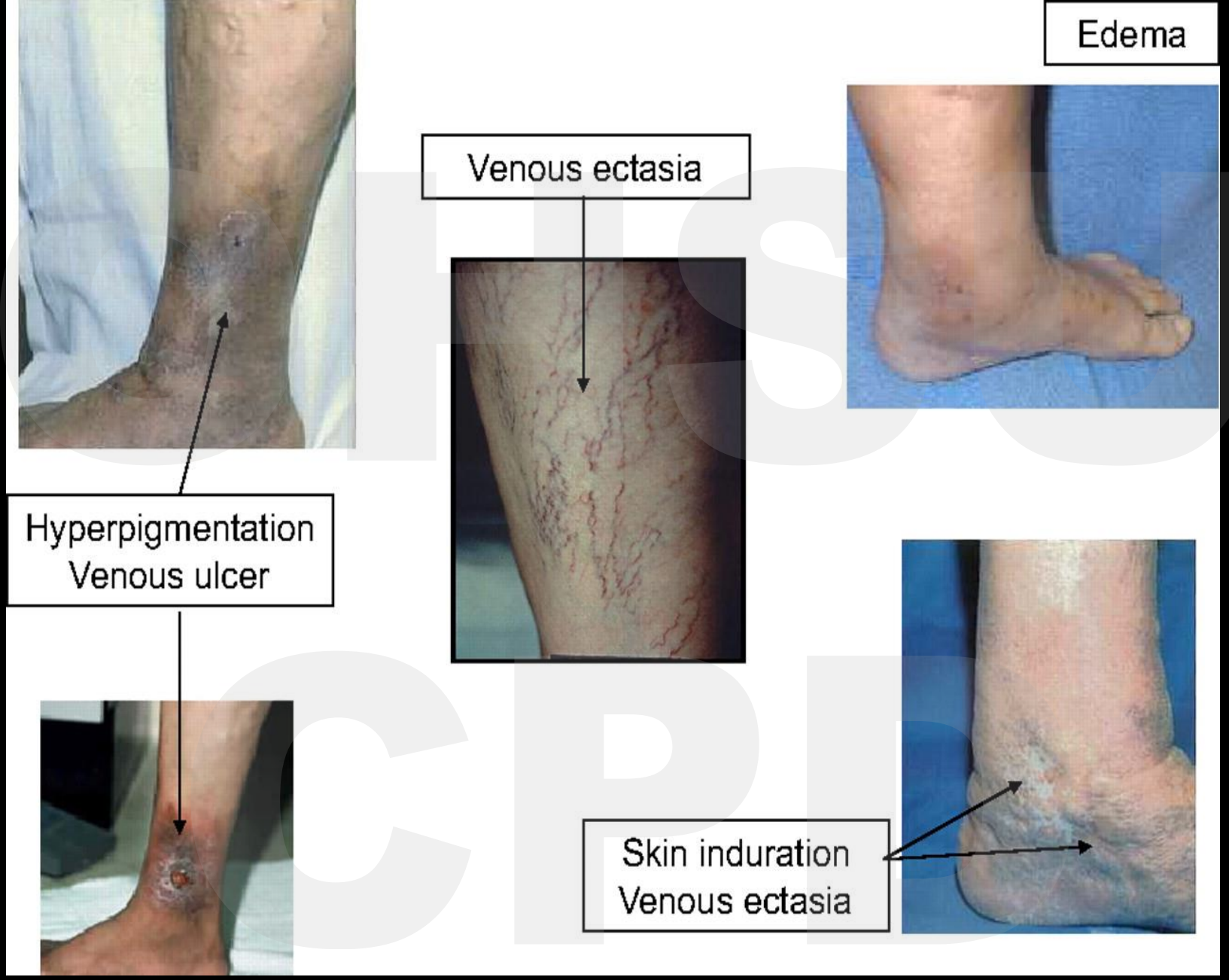
Consultant/Research – none

Author – UpToDate (Iron)

Your patients been diagnosis with a thrombosis – now what?

Post-Thrombotic Syndrome

- Common complication of DVT
- 20-50% of all patients
- 5-10% severe
- Can be disabling



Blood, 19 November 2009, Vol. 114:4624-4631.

PTS: Risk Factors

- Common femoral or iliac vein thrombosis
- Previous DVT
- High BMI
- Older age
- Inadequate initial anticoagulation

Prevention

- Prevent thrombosis!
- Keep the patient active!
- DOACs
  - 4 studies show less PTS
- Stockings controversial but…

Compression Stockings

- Apply within 24 hours
- 20-30mmHg
- Wear at least 6 months
- Replace every 3 months
- Apply in bed first thing

Therapy of PTS

- Compression stockings
  - Knee high
- Leg elevation
- Horse chestnut seed extract
  - BID for a 12 weeks trial
- Treat neuropathic pain
- Leg massage
- Venous stenting (?)

Post-PE Syndrome?

- 50% of patients with PE report dyspnea 6 months later
- 20-70% state health status worse
- Seemingly not related to clot residual or scarring
- Chest pain/discomfort very common
- Warn/reassure patients
- “Cardiac” rehab

Duration of Therapy

Idiopathic versus provoked thrombosis is **the biggest** determinant of risk of recurrent thrombosis

Duration of Therapy

- Not all thrombosis are the same
- Can stratify patients by:
  - Site of thrombosis
  - Circumstances of thrombosis
    - Most important!
  - Presence of hypercoagulable states

Superficial Thrombophlebitis

- Very common
- Strong inflammatory component
- Wide range of therapeutic options

STP: LMWH

STTEPS

- Symptomatic STP
- 8-12 day of therapy
  - Placebo: 30.6% (3.6%)
  - NSAIA: 14.9% (2.1%)
  - 40 mg LMWH: 8.3% (0.9%)
  - 1.5 mg/kg LMWH: 6.9% (1.0%)

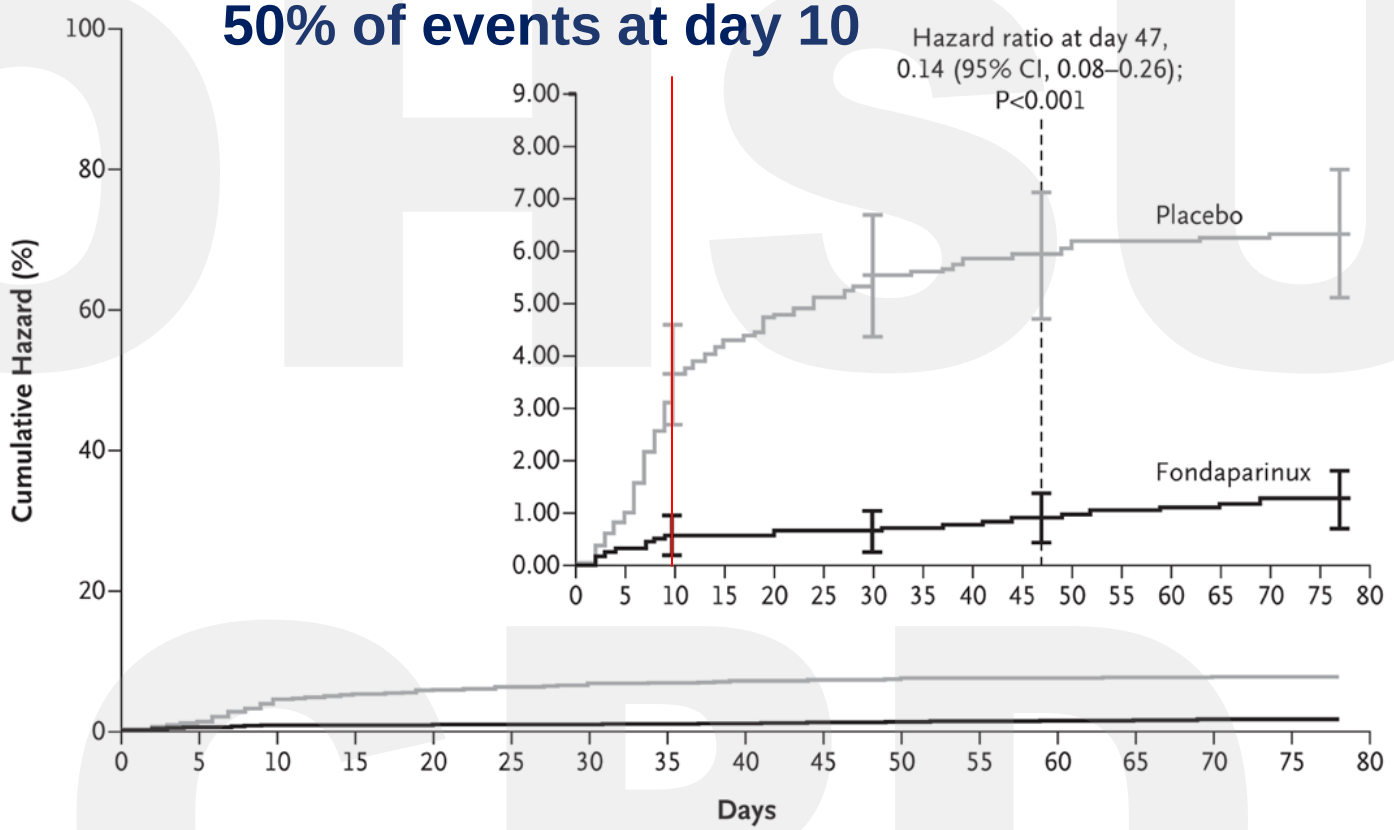
Vesalio Study Group

- Greater saphenous vein STP
- One month of therapy
  - Prophylactic dose: 7.2%
  - Treatment dose: 7.2%

Superficial Thrombophlebitis

- Fondaparinux 2.5 mg/day x 45 days
  - Endpoint: F: **0.9%** P: **5.9%**
  - DVT/PE F: **0.2%** P: **1.5%**
  - No difference in bleeding
  - Need to treat 88 patients to prevent one DVT/PE
  - NEJM 363:1222-32, 2010

50% of events at day 10



No. at Risk	Day 10±2	Day 30±2	Day 45±2	Day 75±2
Placebo	1437	1399	1388	1330
Fondaparinux	1483	1477	1468	1410

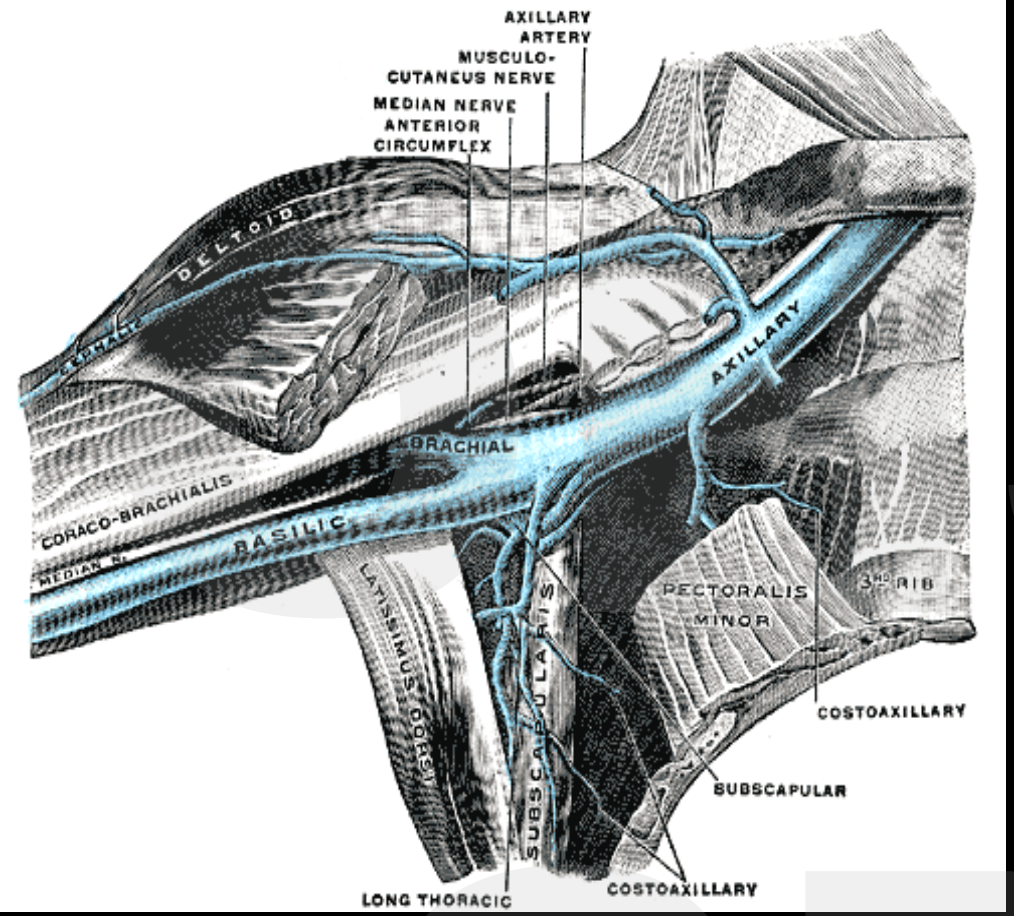
Decousus H et al. N Engl J Med 2010;363:1222-1232

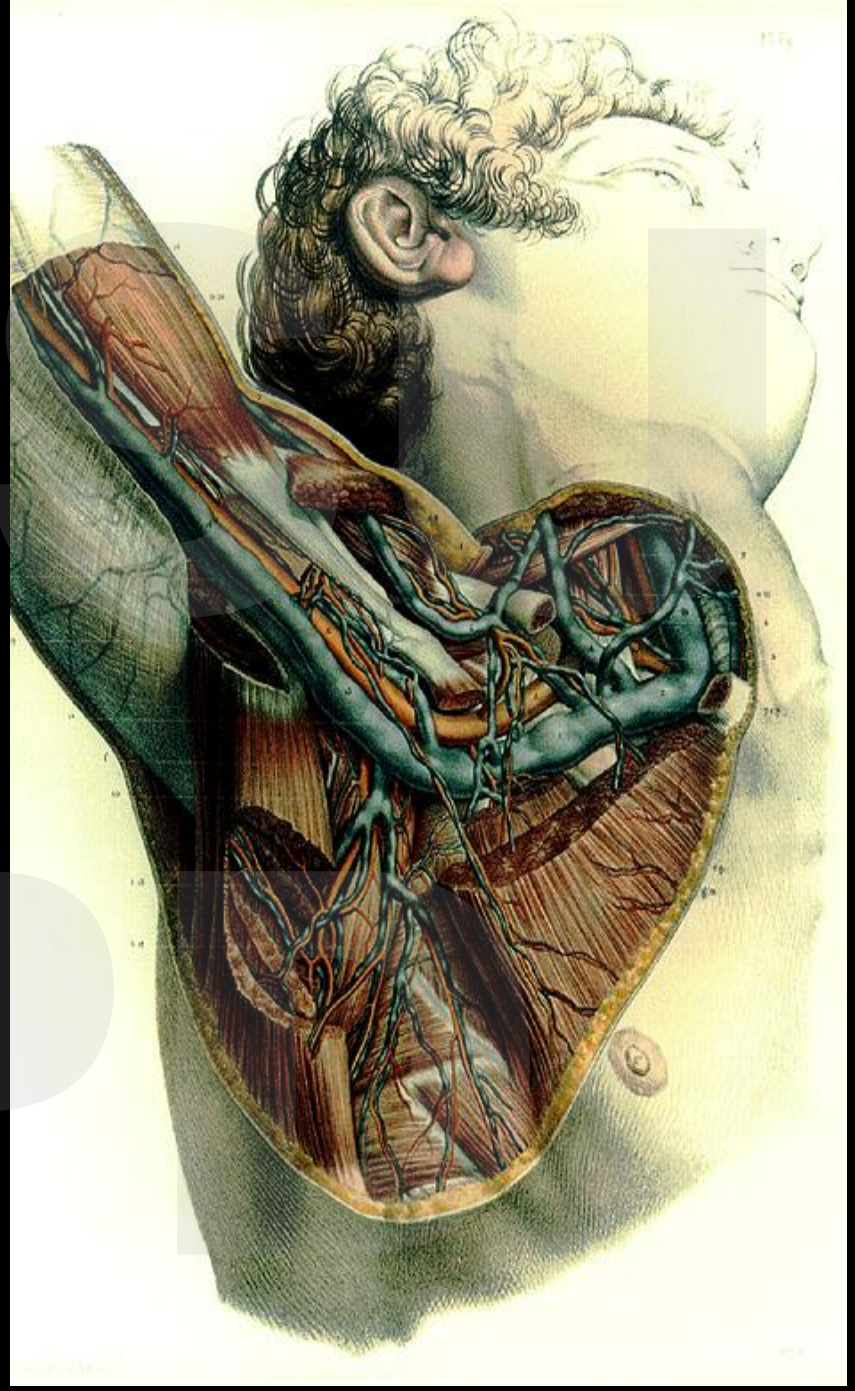
Superficial Thrombophlebitis

- Small and distal: NSAIA and heat
- Painful, large (> 5cm) or greater saphenous vein
  - At least 10 days of prophylactic dose LMWH or fondaparinux
- Role of DOAC uncertain
  - ? DVT rate

Upper Extremity Thrombosis

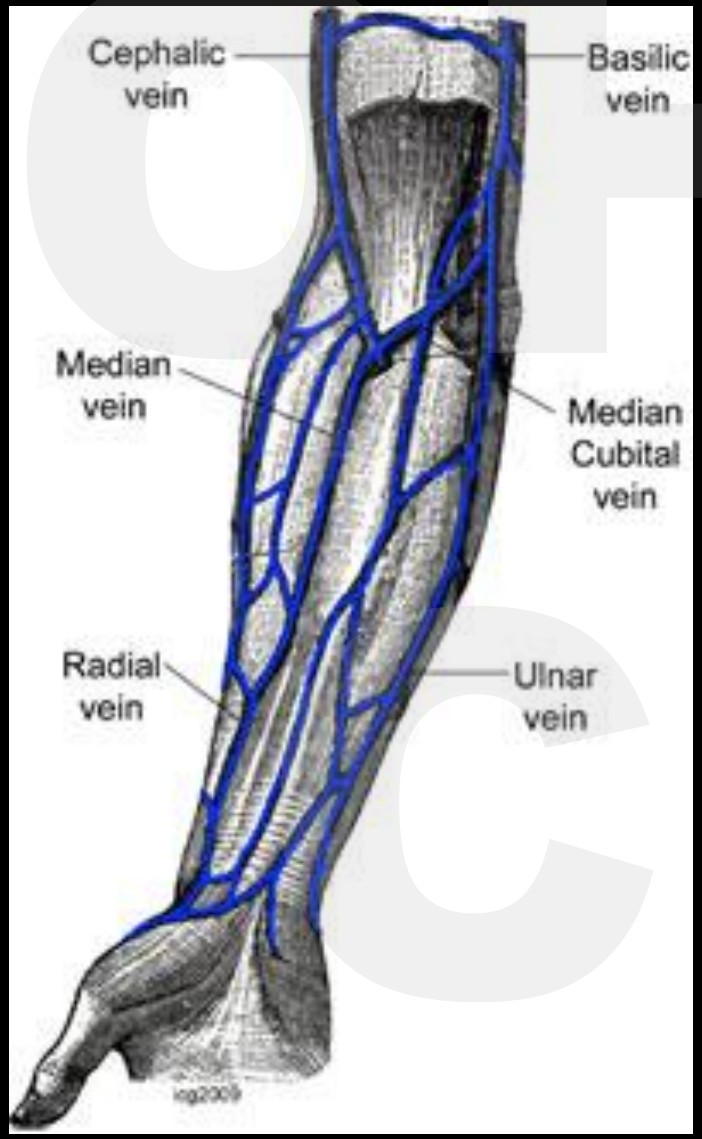
- Mechanical defects
  - Catheter
    - PICC **3-5%**
  - Local venous trauma
- Prophylaxis ineffective
- Low risk of serious sequela

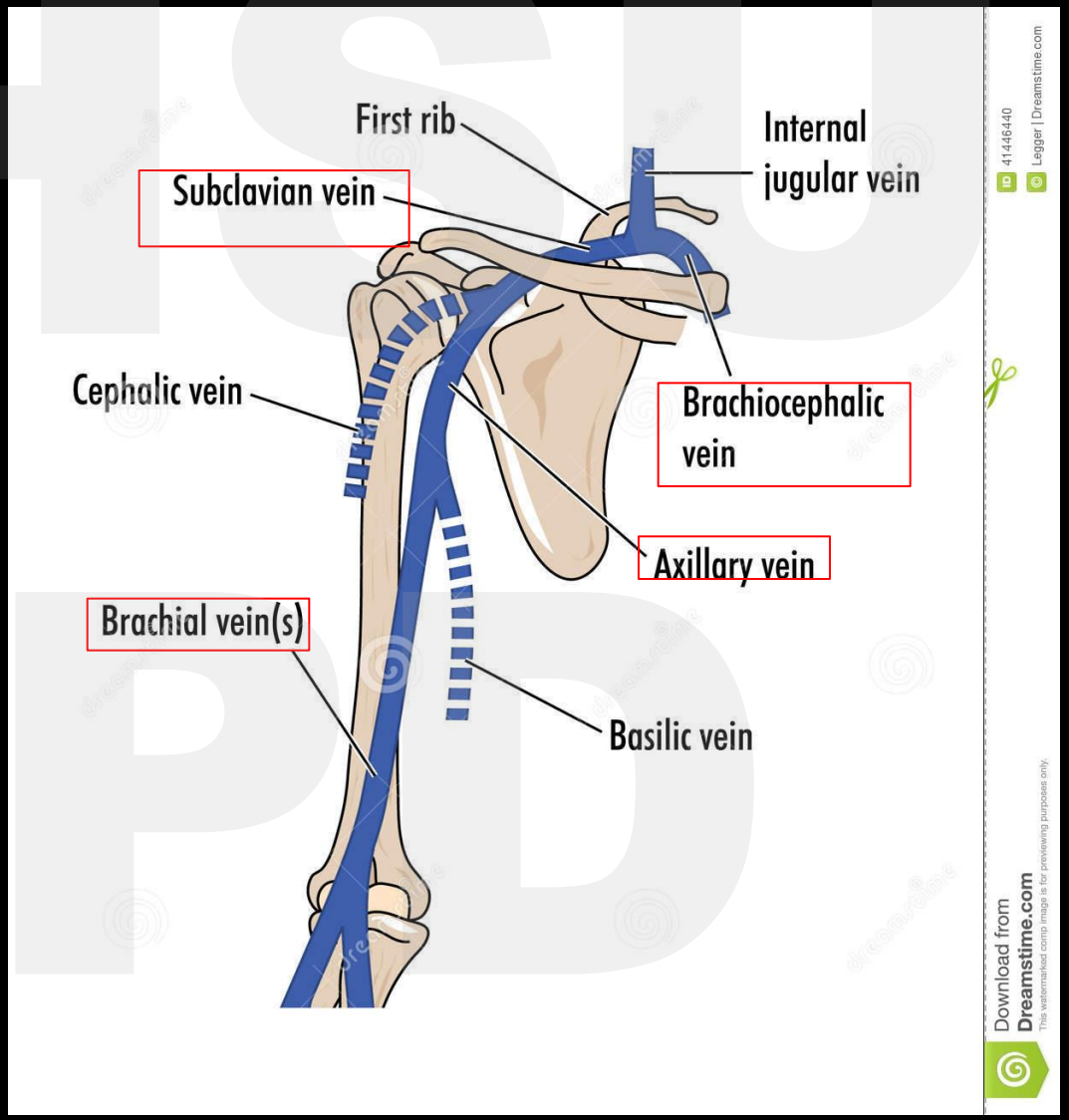

AXILLARY ARTERY
MUSCULO-CUTANEUS NERVE
MEDIAN NERVE
ANTERIOR CIRCUMFLEX
DELTOID
CEPHALIC
AXILLARY
BRACHIAL
CORACO-BRACHIALIS
BASILIC
MEDIAN N.
LATISSIMUS DORSI
SUBSCAPULARIS
PECTORALIS MINOR
3RD RIB
COSTOAXILLARY
SUBSCAPULAR
LONG THORACIC
COSTOAXILLARY



Upper Extremity Thrombosis

- Therapy: PICC Catheter
  - Key is removing catheter
  - No new one for at least 10 days
  - Benefit of anticoagulation uncertain
    - 25% rate of bleeding
  - Remember many are superficial thrombosis





Upper Extremity Thrombosis

- Therapy: Non-PICC Catheter
  - Line can be removed
    - –Assess need for anticoagulation
  - Line cannot be removed
    - –3 months anticoagulation
    - –High rates of serious bleeding

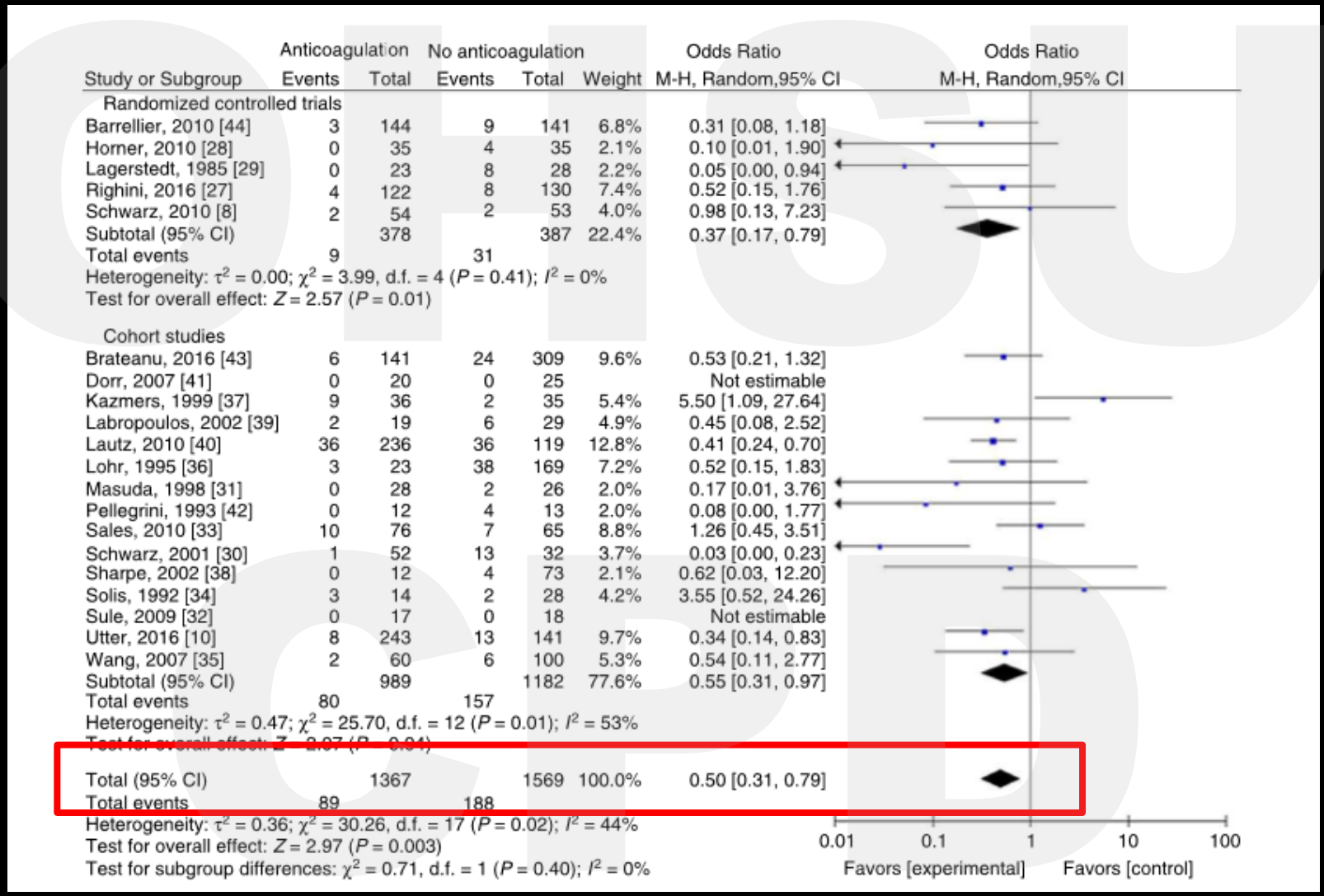
Upper Extremity Thrombosis

- "Spontaneous"
  - 3 months anticoagulation
  - Look for underlying vascular defects
  - Consider thrombolytic therapy
    - ~75% with underlying lesions

Calf Vein Thrombosis

- High risk of progression
  - Up to 10% progression
  - PE rate 2-3%
- 12 weeks therapy for most patients

Calf Vein Thrombosis Therapy



Study or Subgroup	Anticoagulation Events	Total	No anticoagulation Events	Total	Weight	Odds Ratio M-H, Random,95% CI
Randomized controlled trials						
Barrellier, 2010 [44]	3	144	9	141	6.8%	0.31 [0.08, 1.18]
Horner, 2010 [28]	0	35	4	35	2.1%	0.10 [0.01, 1.90]
Lagerstedt, 1985 [29]	0	23	8	28	2.2%	0.05 [0.00, 0.94]
Righini, 2016 [27]	4	122	8	130	7.4%	0.52 [0.15, 1.76]
Schwarz, 2010 [8]	2	54	2	53	4.0%	0.98 [0.13, 7.23]
Subtotal (95% CI)		378		387	22.4%	0.37 [0.17, 0.79]
Total events	9		31			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.99$, d.f. = 4 ($P = 0.41$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.57$ ($P = 0.01$)						
Cohort studies						
Brateanu, 2016 [43]	6	141	24	309	9.6%	0.53 [0.21, 1.32]
Dorr, 2007 [41]	0	20	0	25		Not estimable
Kazmers, 1999 [37]	9	36	2	35	5.4%	5.50 [1.09, 27.64]
Labropoulos, 2002 [39]	2	19	6	29	4.9%	0.45 [0.08, 2.52]
Lautz, 2010 [40]	36	236	36	119	12.8%	0.41 [0.24, 0.70]
Lohr, 1995 [36]	3	23	38	169	7.2%	0.52 [0.15, 1.83]
Masuda, 1998 [31]	0	28	2	26	2.0%	0.17 [0.01, 3.76]
Pellegrini, 1993 [42]	0	12	4	13	2.0%	0.08 [0.00, 1.77]
Sales, 2010 [33]	10	76	7	65	8.8%	1.26 [0.45, 3.51]
Schwarz, 2001 [30]	1	52	13	32	3.7%	0.03 [0.00, 0.23]
Sharpe, 2002 [38]	0	12	4	73	2.1%	0.62 [0.03, 12.20]
Solis, 1992 [34]	3	14	2	28	4.2%	3.55 [0.52, 24.26]
Sule, 2009 [32]	0	17	0	18		Not estimable
Utter, 2016 [10]	8	243	13	141	9.7%	0.34 [0.14, 0.83]
Wang, 2007 [35]	2	60	6	100	5.3%	0.54 [0.11, 2.77]
Subtotal (95% CI)		989		1182	77.6%	0.55 [0.31, 0.97]
Total events	80		157			
Heterogeneity: $\tau^2 = 0.47$; $\chi^2 = 25.70$, d.f. = 12 ($P = 0.01$); $I^2 = 53\%$						
Test for overall effect: Z = 2.07 (P = 0.04)						
Total (95% CI)		1367		1569	100.0%	0.50 [0.31, 0.79]
Total events	89		188			
Heterogeneity: $\tau^2 = 0.36$; $\chi^2 = 30.26$, d.f. = 17 ($P = 0.02$); $I^2 = 44\%$						
Test for overall effect: $Z = 2.97$ ($P = 0.003$)						
Test for subgroup differences: $\chi^2 = 0.71$, d.f. = 1 ($P = 0.40$); $I^2 = 0\%$						

Journal of Thrombosis and Haemostasis, **15**: 1142–1154

Calf Vein Thrombosis Therapy

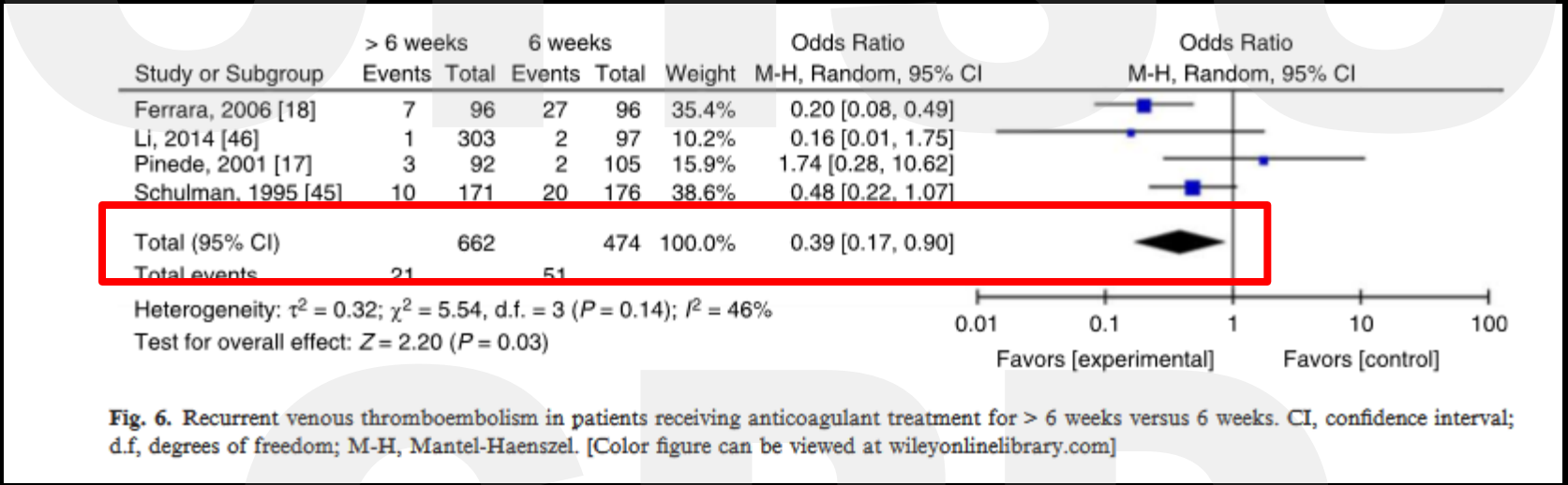
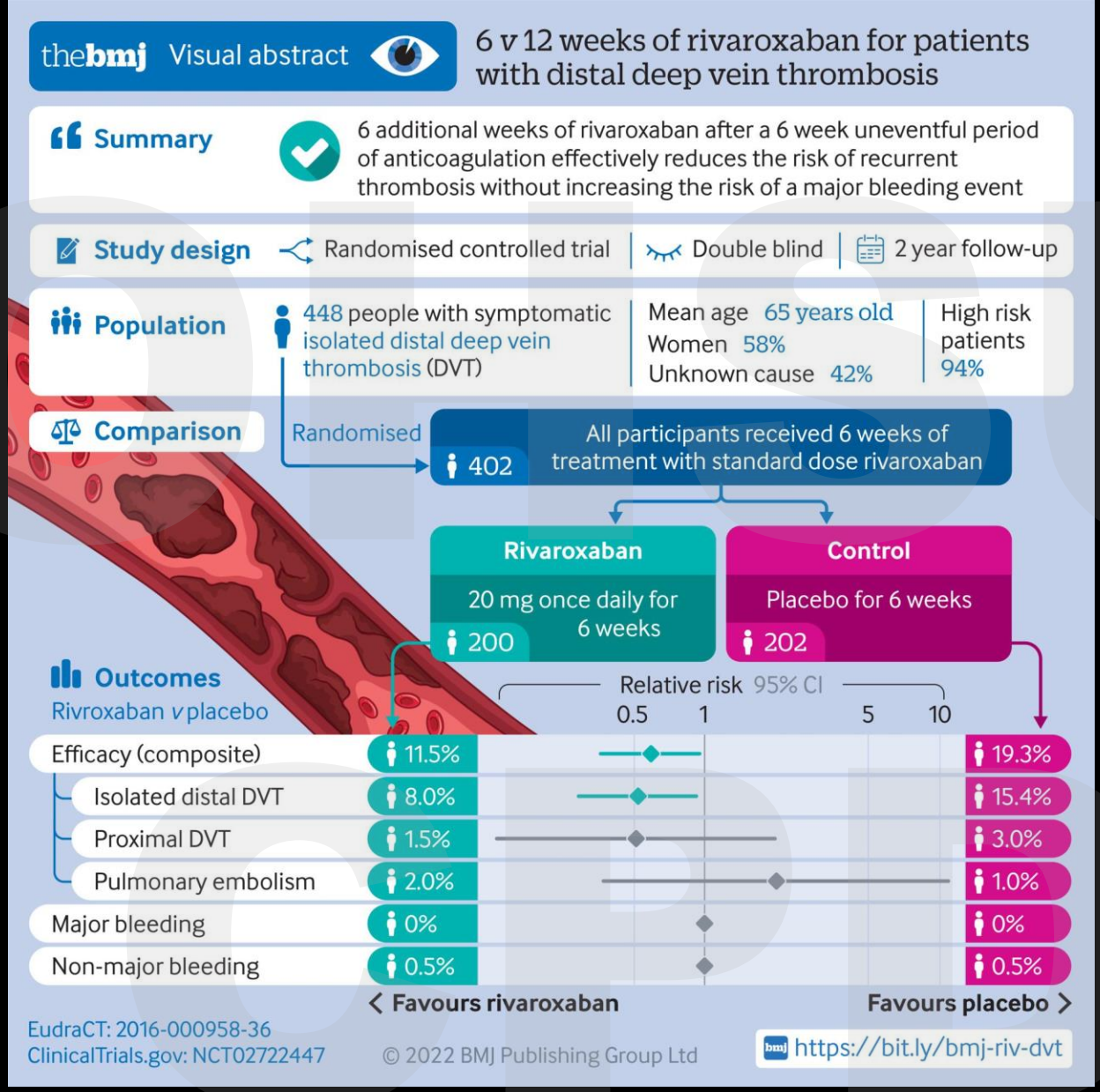


Fig. 6. Recurrent venous thromboembolism in patients receiving anticoagulant treatment for > 6 weeks versus 6 weeks. CI, confidence interval; d.f, degrees of freedom; M-H, Mantel-Haenszel. [Color figure can be viewed at wileyonlinelibrary.com]

Journal of Thrombosis and Haemostasis, **15**: 1142–1154

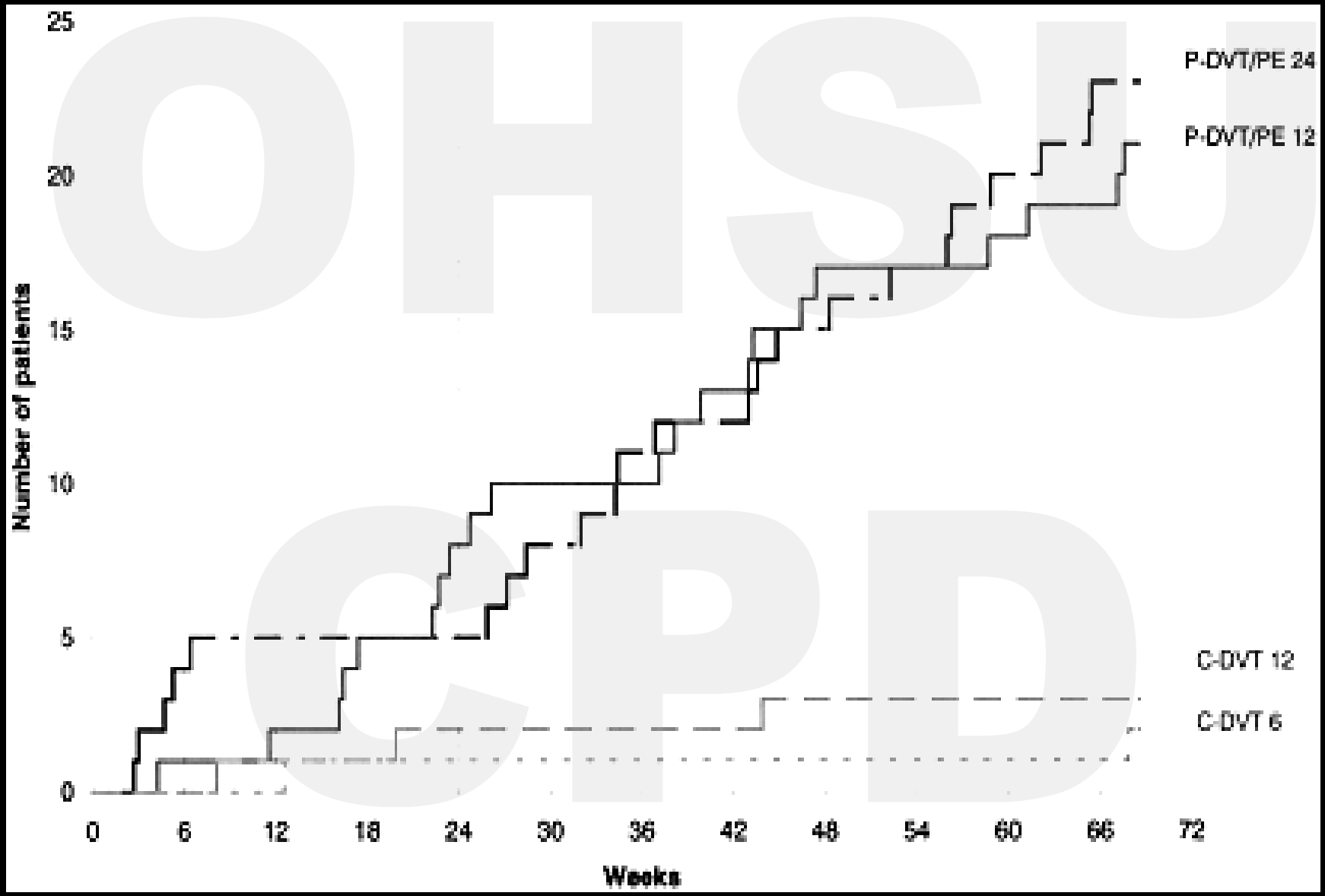


Walter Ageno et al. BMJ 2022;379:bmj-2022-072623

Duration of Therapy: Proximal DVT

- 3 months
  - Provoked DVT
    - Especially estrogen related
- No benefit with 6 months except more bleeding
- Obtain scan at end of therapy for new baseline
  - J Thromb Haemost. 2011 Dec;9(12):2406-10

Proximal DVT



Circulation, May 2001; 103: 2453 - 2460.

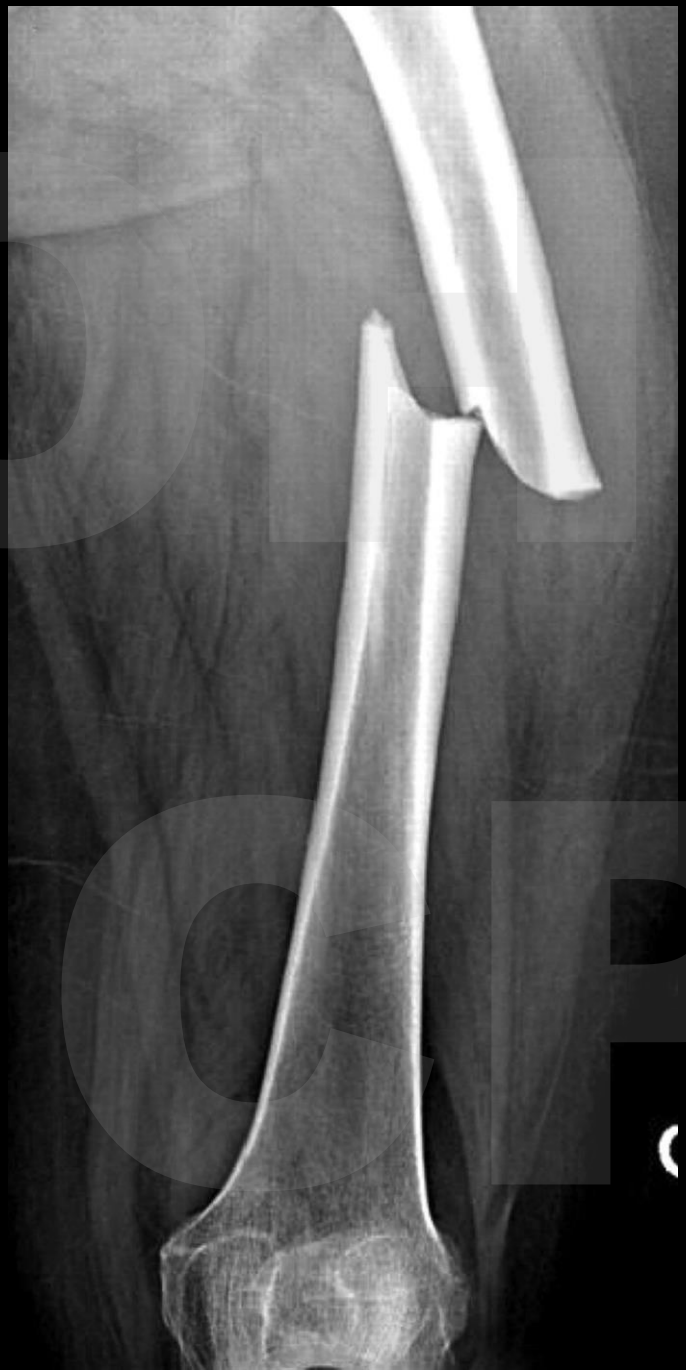
Residual Thrombosis

- 3 months – 80.5%
- 6 months - 61%
- 12 months – 42%
- 24 months – 31%
- 36 months – 27%

Prandoni Annals IM 2002

What is Provoked??

- Major
  - Limb fracture
  - Major trauma
  - Big surgery
  - Estrogen
    - Pregnancy
    - Estrogen-containing contraception
    - HRT
  - Travel



www.orthobullets.com/trauma

Idiopathic

- No MAJOR provoking factor
- Minor ones common
  - Twisted ankle etc..

Immobilization

- Classic is bedrest > 72 hrs
- Limb in cast
- Total immobilization > ~ 4 hours
  - Especially > 10-12 hours

Duration of Therapy

- What is an Idiopathic Thrombosis?
  - No trauma, surgery or hospital stay for 1-3 months
  - No estrogens
  - No long travel (?)
  - No cancer or major risk factors
  - Exact definition controversial

1st Idiopathic VTE

- High rates (30-40%) of recurrence off anticoagulation
- Multiple RCTs show benefit of long term anticoagulation
  - Marked increase in recurrence when stopping anticoagulation

BMJ 2019 Meta-analysis

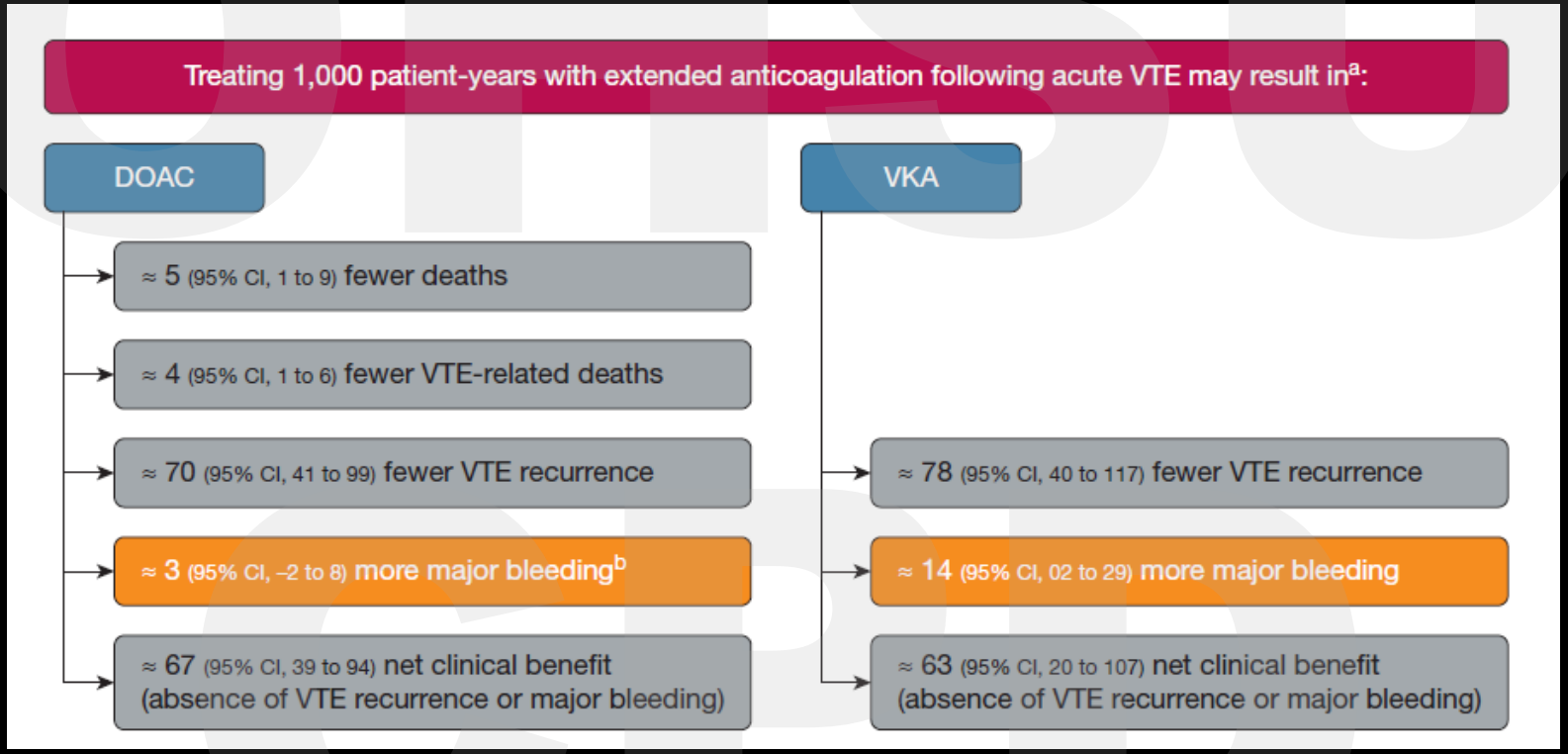
Year	Risk	Cumulative Incidence
1 Year	10.3%	-
2 year	6.3%	16%
3-5 years	3.8%/year	25% 5 years
6-10 years	3.1/year	36% 10 years

Case fatality rate for recurrence 4%

Distal thrombosis 1/10th of risk

BMJ 2019: 366:4364

Extended Therapy



Chest 155:1199-1216, 2019

Two Phases of VTE Therapy

- Active phase (3 months)
  - Prevents reactivation of initial thrombosis
- Secondary prevention (> 3 months)
  - Prevents new thrombosis
  - Need to identify patients who will benefit

- J Thromb Haemo 2012: 10: 507–5

D-Dimers

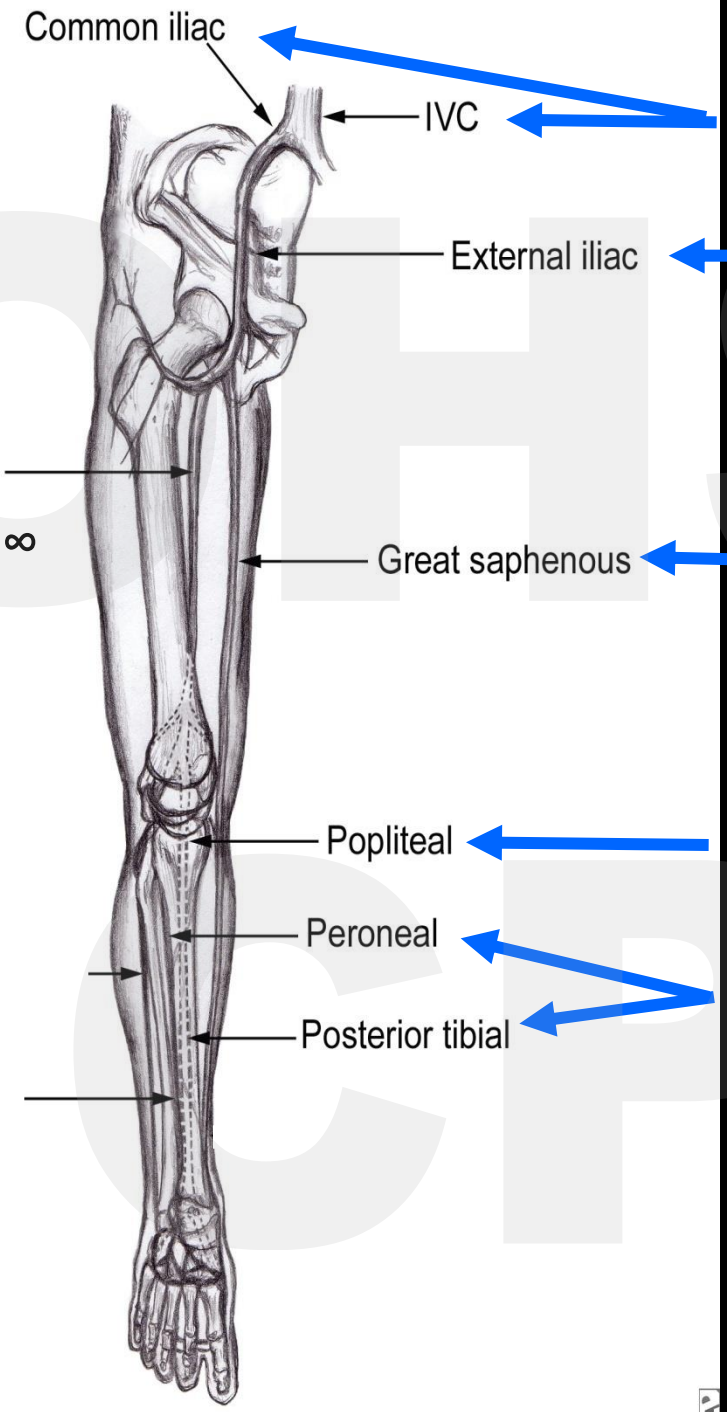
- D-dimers checked off therapy to predict risk
- Meta-analysis
  - 7 studies
  - Positive D-Dimer: 10%/yr
  - Negative D-Dimer: 2.9 - 4.0%/yr
- Unclear if repeat testing helps
- Most recent study showed high rates of recurrence with negative D-dimer 5%/yr

Idiopathic VTE

- No good prediction rules
  - Negative D-dimer - NOT predictive
  - Thrombus resolution – NOT predictive
- Still need better prediction rules!
- Safer anticoagulants is shifting balance toward longer treatment

Duration of Therapy

- Indefinite
  - >1 DVT (except upper ext)
  - Acquired hypercoagulable states
  - Idiopathic unusual site
  - Idiopathic severe pulmonary embolism
- 3 months
  - Provoked pulmonary embolism



3 months - ∞

3 months - ∞

3 months - ∞

14 days
(prophylactic dose)

3 months - ∞

3 months

Pregnancy

- Needs weight based LMWH
  - 1 mg/kg BID
- No value in measuring levels
- Hold 24 hours before delivery
- Restart 6-12 after delivery

Breast Feeding

- Warfarin – ok
- LMWH – ok
- DOAC – NO!

What about Hypercoagulable States?

Hypercoagulable State

- Clear risk factor for 1st VTE
- No evidence with classic genetic states predict recurrence
- Multiple guidelines against checking in provoked thrombosis

Thrombophilia Work-Ups

- Don’t screen for genetic causes
  - For provoked thrombosis
  - Arterial thrombosis
  - Upper extremity thrombosis
- ~$1200

Lower Dose DOACs?

- Older data for lower doses in chronic therapy of VTE
  - LMWH
  - Ximelagatran
  - Did not work for warfarin

Apixaban Results

	Apixaban 2.5mg BID (840)	Apixaban 5mg BID (813)	Placebo (829)
Recurrent VTE	32 (3.8%)	34 (4.2%)	96 (11.6%)
Any Bleeding	27 (3.2%)	35 (4.3%)	19 (2.3%)
Major Bleeding	2 (0.2%)	1 (0.1%)	4 (0.5%)

N = 2482 with VTE (33% PE)

N Engl J Med 2013; 368:699-708

Rivaroxaban Results

	Rivaroxaban 20mg (1107)	Rivaroxaban 10mg (1127)	Aspirin 100mg (1131)
Recurrent VTE	17 (1.5%)	13 (1.2%)	50 (4.4%)
Any Bleeding	196 (17.8%)	160 (14.2%)	143 (12.8%)
Major Bleeding	6 (0.5%)	5 (0.4%)	3 (0.3%)

N = 3365 50% with PE

N Engl J Med 2017; 376:1211-1222

RENOVE Trial

- RCT of patients with thrombosis
- Randomized 6-24 to standard vs low dose anticoagulation
- N = 2768
- Power for bleeding superiority

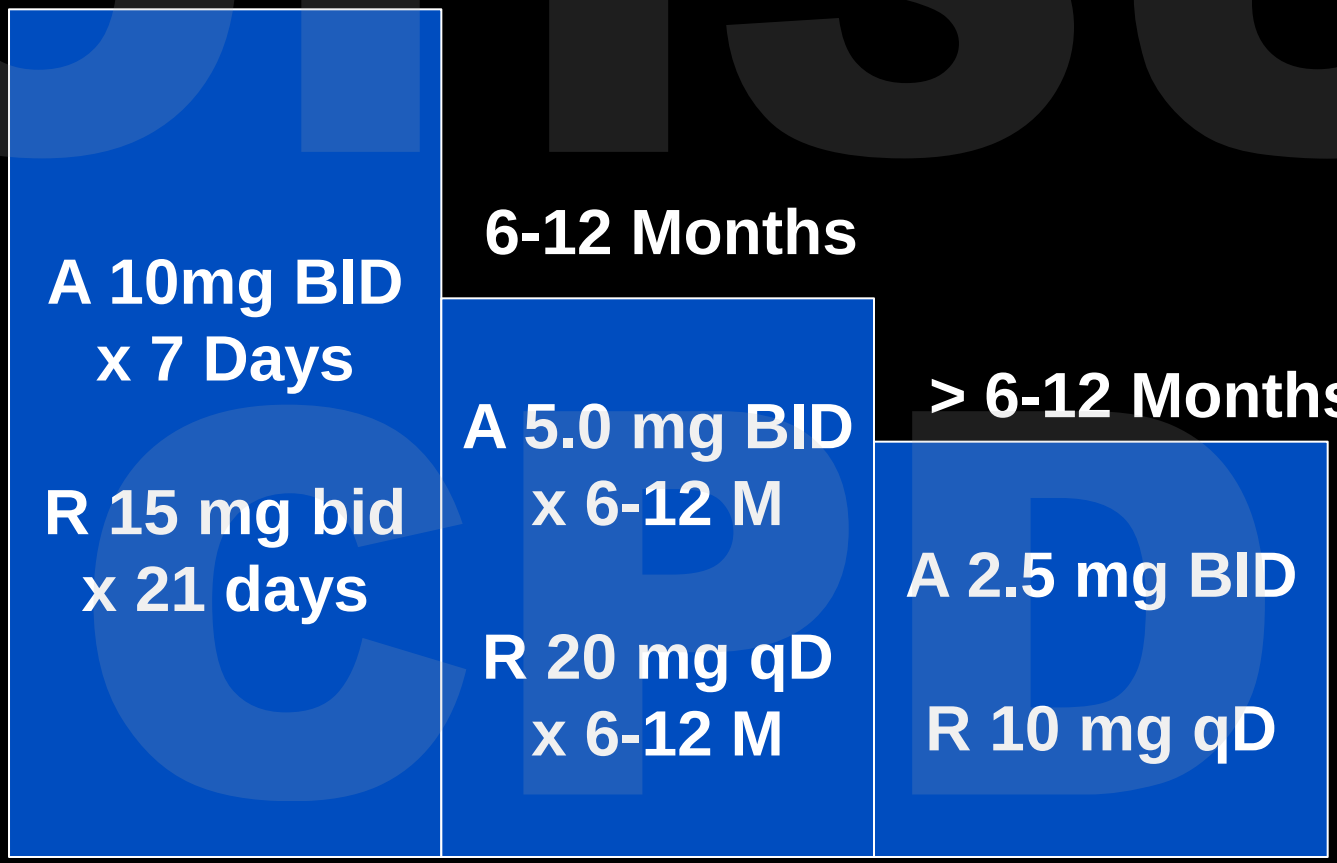
ASH 2024

	Full Dose N = 1383	Half Dose N = 1385	HR
Recurrent VTE	13 (1.9%)	19 (2.2%)	1.32 (NS)
Clinical Bleeding	154 (15.2%)	96 (9.9%)	0.61 (p <0.5)
Composite	166 (16.5%)	113 (16.7%)	0.67 (p < 0.5)

Lower Dose Therapy

- Only for chronic venous thrombosis!!
- NOT
  - Atrial fibrillation
  - Cancer
  - Bad thrombophilia
  - Visceral vein thrombosis

DOAC VTE Stepped Care



Direct Oral Anticoagulants

- First line therapy for VTE
- Simplified management
- But
  - Patients still need close follow-up
  - Still need to manage anticoagulants
  - Expense an issue

“Break-Through” Clots

- DOACs are not perfect
- Neither are patients…

“Break-Through” Clots

1. Is it a breakthrough clot?
   - New PE in first week ~ 5%
   - DVT can grow on therapy
   - New: new vessel or limb involved
   - PE after 2 weeks

   - Olson SR, RPTH 2019

“Break-Through” Clots

- 2. Was patient taking med?
  - Ideal: levels sent
  - Ok: INR/PTT check
  - Check DOAC dose
  - Ask patient
  - Check pharmacy

“Break-Through” Clots

3. Treatment
   - LMWH
     - If breakthrough LMWH raise dose 25%
   - Warfarin
     - Compliance concerns

Surgery/Procedures

- Increasing data
- Need to know
  - Drug
  - Procedure
  - Renal function

DOACs and Surgery

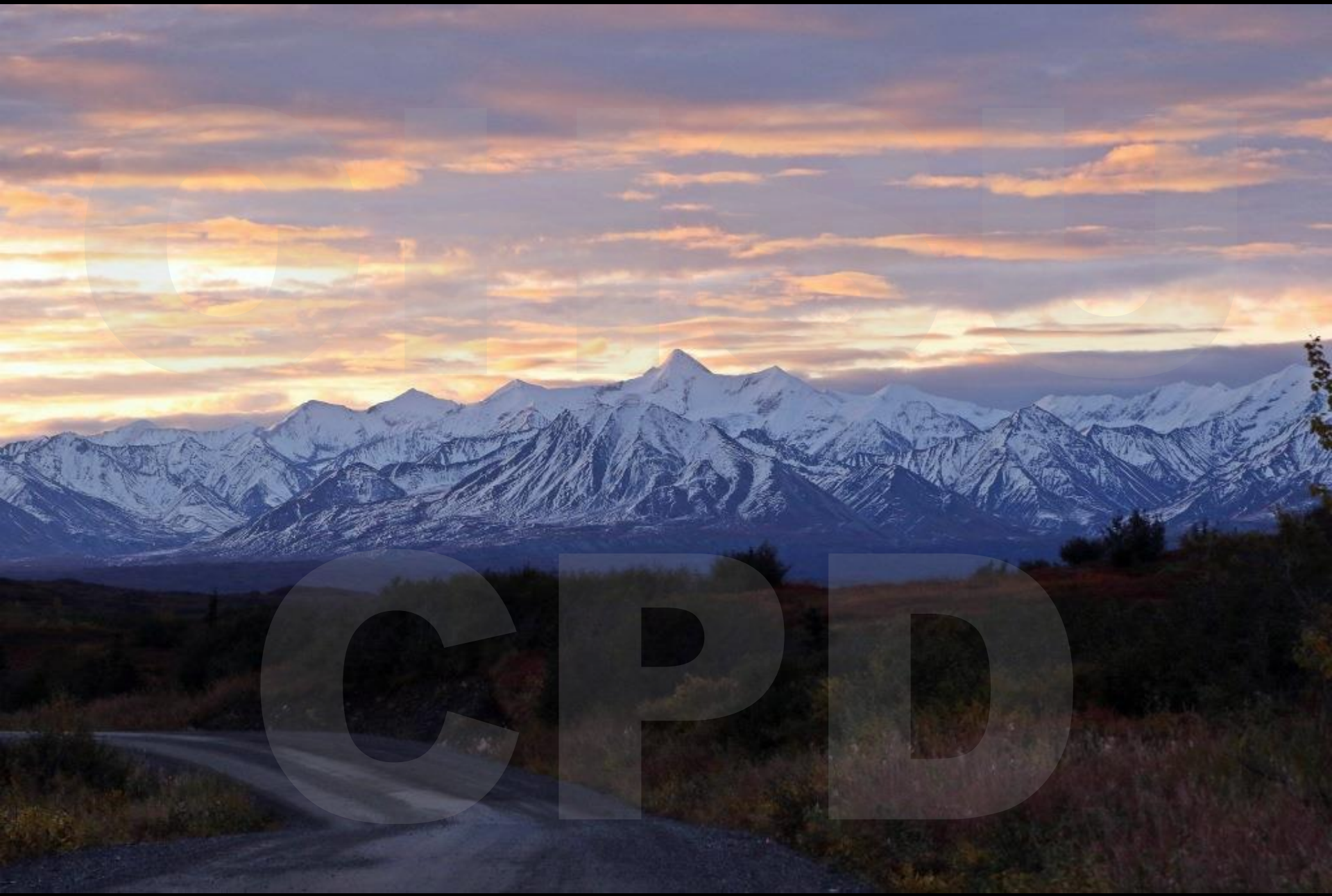
Drug	Surgery	CrCl	-4	-3	-2	-1	Surgery
Apix	Major				Hold	Hold	Hold
	Minor					Hold	Hold
Dabig	Major	>50			Hold	Hold	Hold
		<50	Hold	Hold	Hold	Hold	Hold
	Minor	>50				Hold	Hold
		<50		Hold	Hold	Hold	Hold
Rivarox	Major				Hold	Hold	Hold
	Minor					Hold	Hold

DOACs: Post Surgery

- Treat like LMWH
- Simple – restart next day
- Complex
  - Prophylactic dose
  - Full dose 48 hours or more

Summary

- Keep moving!
- Anticoagulation
  - 3 months or indefinite
- Lower dose DOACs


CPD